New Therapeutic Options for Stroke Prevention in Atrial Fibrillation

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Atrial Fibrillation: Disclosures

- Dr. Jackson
  - Hoechst-Roussel Pharmaceuticals – 10 years (streptokinase)
  - Dupont-Merck Pharmaceuticals – 2 years (warfarin)
  - Bristol-Myers Squibb – 16 years (clopidogrel, apixaban)
    - Pension and stockholder
  - Thomas Jefferson University – 20 months
  - Health Outcomes Insights – 3 years

- Acknowledgement: Some slides courtesy of
  - Geno J Merli, MD, FACP, FHM, FSVM, Professor of Medicine,
    Co-Director Jefferson Vascular Center,
    Senior Vice President and Chief Medical Officer
    Thomas Jefferson University Hospitals

Stroke Prevention in Atrial Fibrillation: Learning Objectives

1. Describe the characteristics of the population needing stroke prevention in chronic atrial fibrillation

2. Review the comparative effectiveness of oral anticoagulant therapeutic options, benefits and risks

3. Explore issues of effectiveness, safety and value from a population health perspective

Outcomes Research: The Purpose

To determine:

- **Do patients benefit?**
  - Warfarin works, but sub-optimally for many
  - New trials and designs (NOACs…)
- **What treatments work best?**
  - Evaluating opportunities for optimal use
  - Considering implications of RE-LY, ROCKET, ARISTOTLE, and Real World Studies…
- **Are health-care resources well spent?**

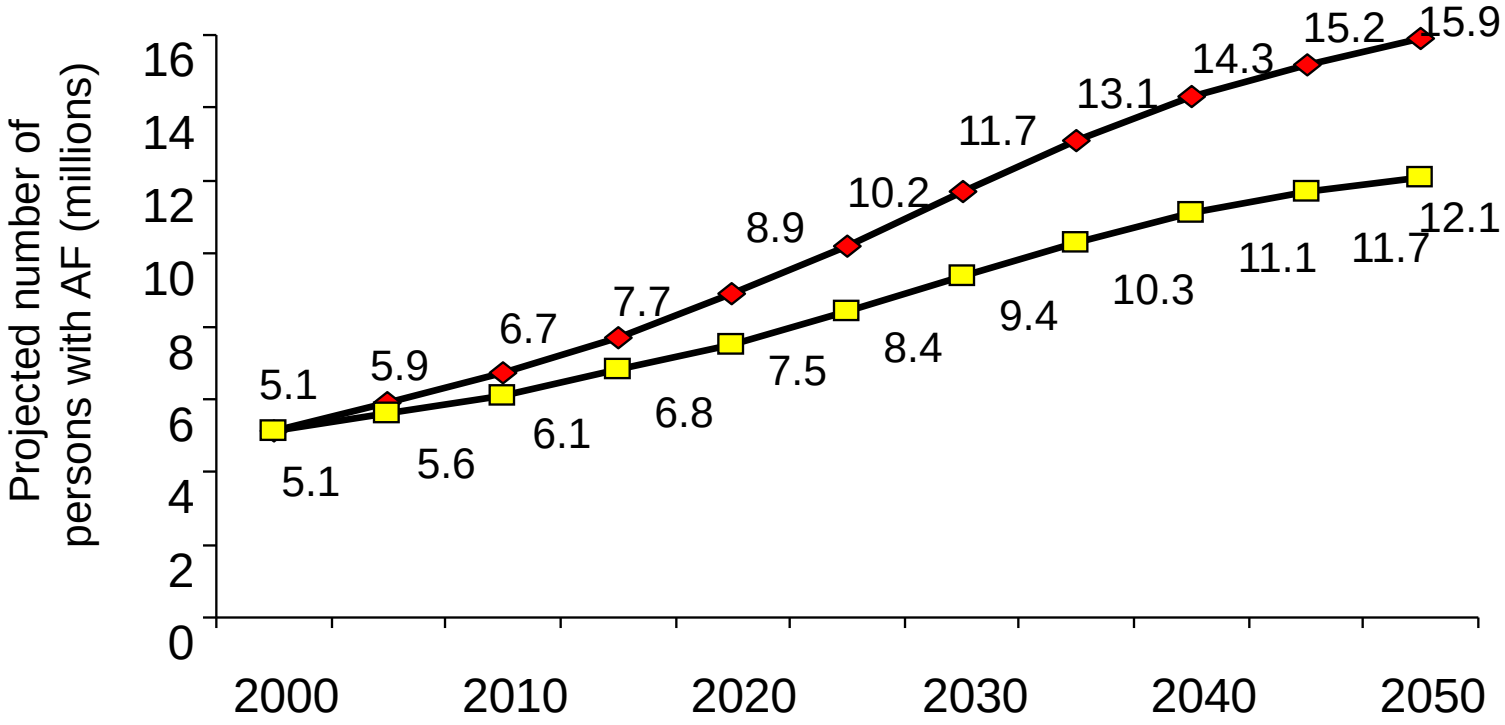
Agency for Health Care Policy & Research, 1990
Agency for Healthcare Research and Quality, 2003

Atrial Fibrillation (AF): Morbidity and Mortality

- ~15% of all strokes occur in people with AF
- Risk of stroke in untreated AF patients averages ~ 5% /yr
- Risk of stroke in AF patients by age group
  - 1.5% in 50 to 59 year age group
  - 23.5% in 80 to 89 year age group
- AF is associated with a 50 to 90% increase in risk of death after adjustment for coexisting CV conditions

Wolf PA, et al. *Stroke* 1991; 22: 983-988
Benjamin EB, et al. *Circulation* 1998;98:946-952.
American Heart Association. *Heart Disease and Stroke Statistics-2006 Update*. Dallas, TX: American Heart Association;2006.

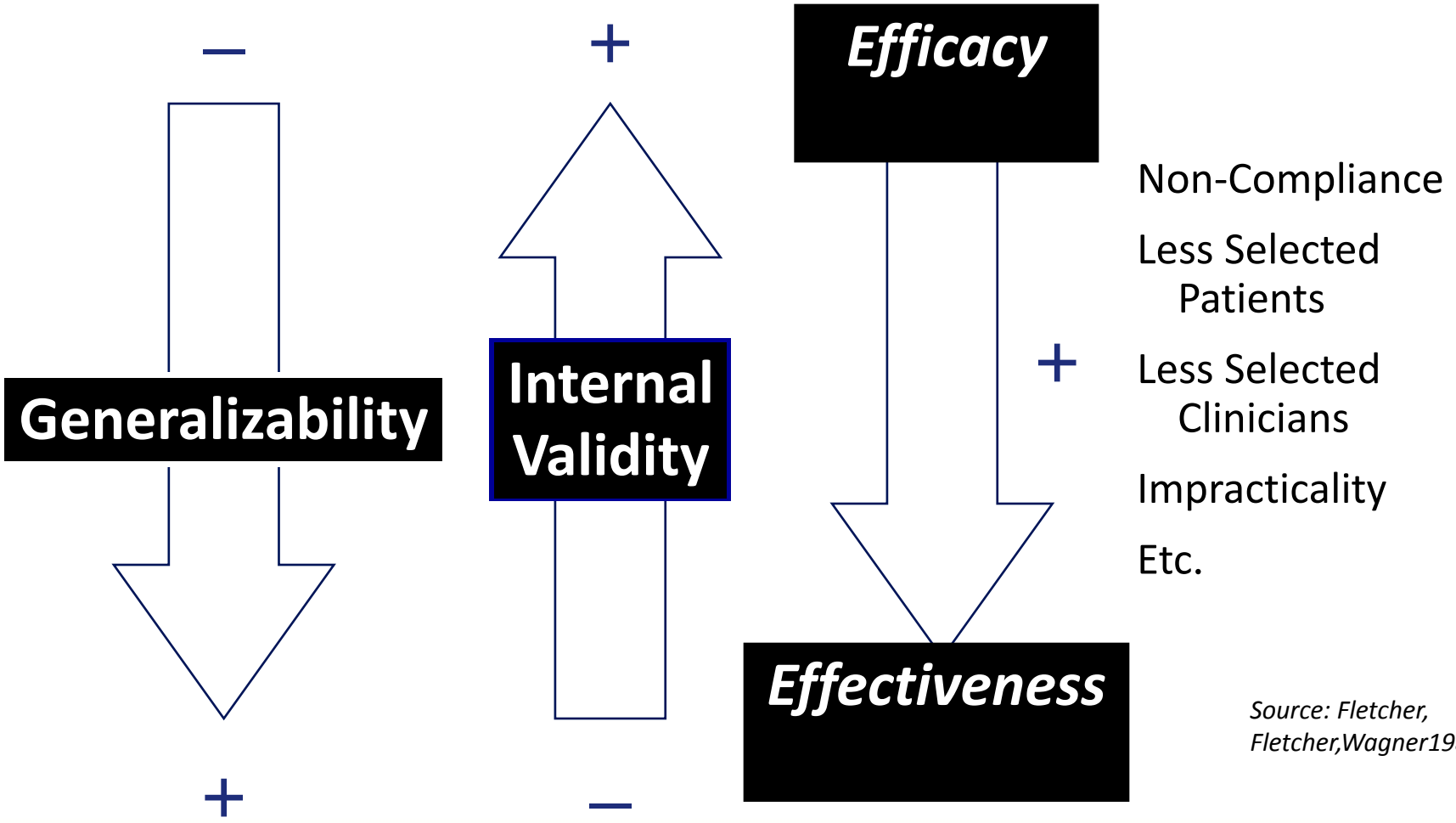
Projected Number of Persons with AF in the U.S. between 2000 and 2050



Assumes no further increase in age-adjusted AF incidence (yellow curve) and assumes a continued increase in incidence rate as evident in 1980 to 2000 (red curve)

Source: Miyasaka Y, et.al. *Circulation* 2006;114:119-125.

Efficacy and Effectiveness



Source: Fletcher, Fletcher,Wagner1988

Historical Efficacy of warfarin in Atrial Fibrillation

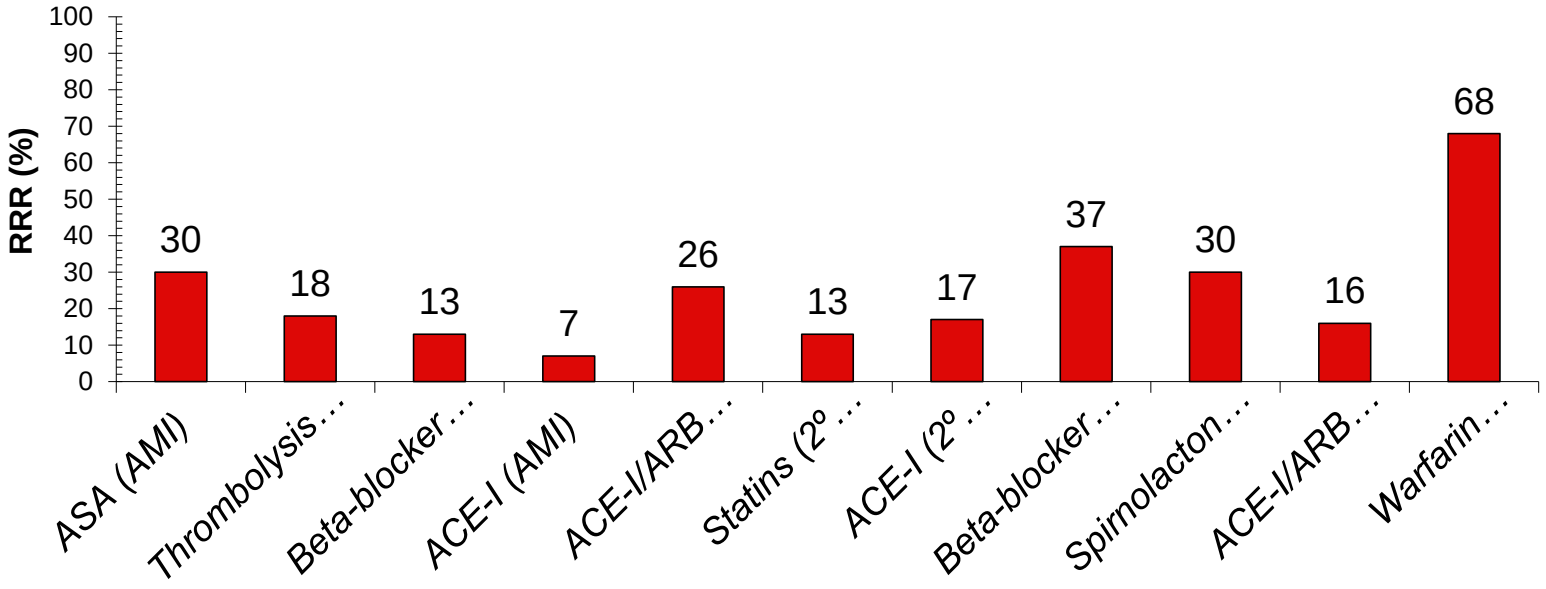
Five Randomized Trials in Non-Rheumatic AF

Study	Warfarin (#)	Cont. (#)	INR	RR	p-Value
AFASAK	335	336	2.8-4.2	**60%**	0.027
SPAF	210	211	2.0-4.5	**67%**	0.01
BAATAF	212	208	1.5-2.7	**86%**	<0.05
CAFA*	187	191	2.0-3.0	**45%**	0.25
SPINAF	260	265	1.4-2.8	**79%**	0.001

* Stopped early due to published positive results

68% overall risk reduction for stroke

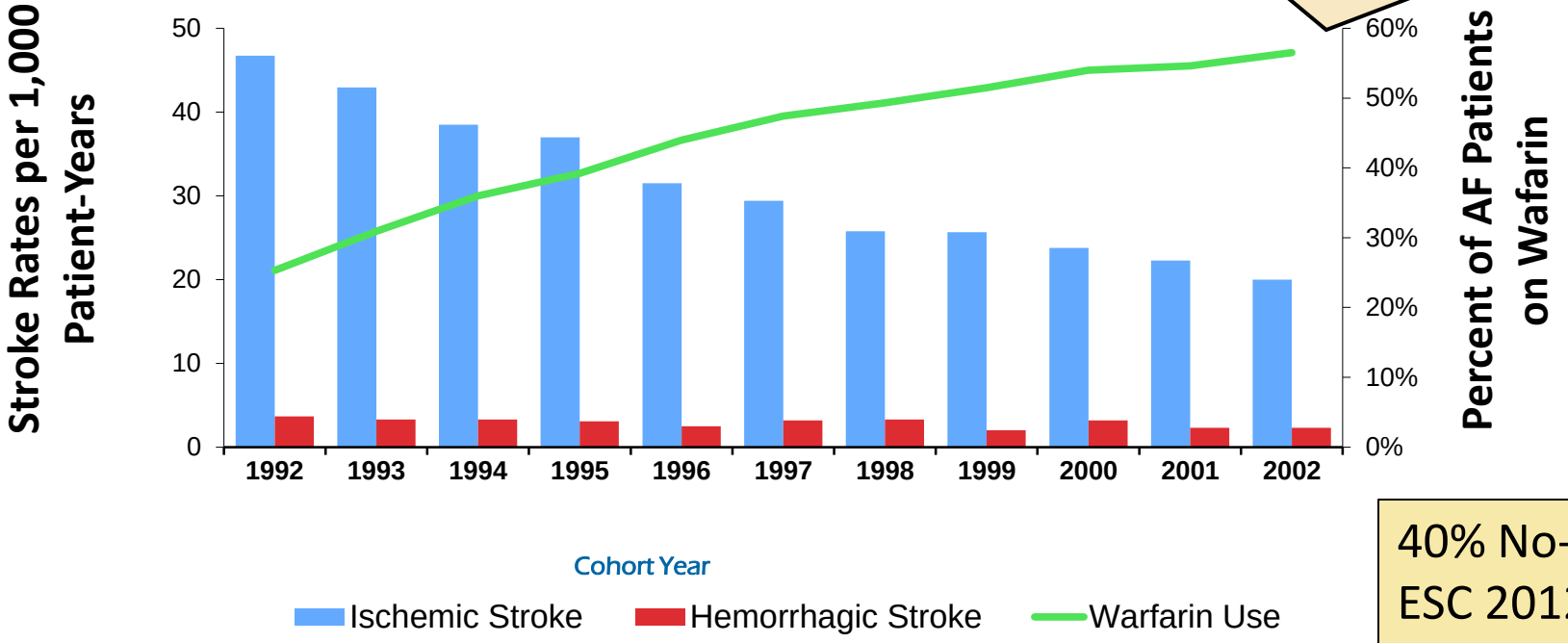
Relative Effects of Various CV Therapies



Source: Granger S, MacMurray J. *JACC* 2006;48:434-7; and Michael Hanna, MD.

Trends in Warfarin Use and Therapeutic Outcomes

36%
AF patients with no identified contraindications not anticoagulated despite moderate or high risk



40% No-Rx
ESC 2012, Garfield Registry

Source: Lakshminarayan K, et al. *Stroke*. 2006;37:1969-1974.

Treatment would prevent 40,000 strokes per year.

Warfarin Liabilities

- Narrow therapeutic range (2.0-3.0).
- Food effect and multiple drug and botanical interactions
- Need for therapeutic monitoring.
- INR of warfarin patients is in the therapeutic range only ~60% of the time, in trials.
- Risk of intracranial hemorrhage, particularly in the elderly.
- **Warfarin is a leading cause of adverse drug events and ER visits.**

Source: Elaine M. Hylek, MD, MPH, Associate Professor of Medicine, Boston University

Factors Influencing Warfarin Under-Use

1. Lack of consensus on perceived or actual barriers to use: e.g., fall risk, prior bleeding, concurrent medicine use, ETOH…

2. Suboptimal candidacy for anticoagulant therapy e.g., comorbidities, polypharmacy, non-adherence…

3. Barriers to INR monitoring-dependence on caregivers, logistical constraints, cost, hassle

4. Inability to tolerate therapy long-term

Source: Elaine M. Hylek, MD, MPH, Associate Professor of Medicine, Boston University

Adherence to Quality Indicators: Conditions

Condition	%
Breast cancer	76
Prenatal care	73
Hypertension	65
CHF	64
Depression	58
Asthma	53
Diabetes mellitus	45
Atrial fibrillation	25
Hip fracture	23
Alcohol dependence	11

Source: McGlynn EA, et.al. *NEJM* 2003;348:2635-45

Perceived or Actual Barriers to Warfarin Use in Atrial Fibrillation Based on Electronic Medical Records

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[2] Indiana University School of Medicine, Indianapolis, Indiana, USA

[3] Bristol-Myers Squibb, Lawrenceville, NJ, USA

[4] Thomas Jefferson University, Philadelphia, PA, USA

Presented: European Society of Cardiology, 2009
American Heart Association, 2009

Published: *American Journal of Therapeutics,* 2012;19:330-337.

This study was funded by Bristol-Myers Squibb and Pfizer Inc.

Methods: Study Population

- Inclusion criteria
  - New-onset NVAF between 1998 and 2007
    - Defined as first encounter (hospital or office visit) with AF stored in the RMRS

- Exposure: Warfarin (vitamin K antagonist [VKA])
  - Hospital/Clinic pharmacy transaction records

    or
  - Physician Order Entry System (Gopher)[1]
    - An electronic version of a prescription

[1]McDonald CJ, Tierney WM. The Medical Gopher—a microcomputer system to help find, organize and decide about patient data. *West J Med* 1986;145:823-9.

Source: Rosenman, ESC and AHA 2009

Methods: Identification of Barriers

Are these patients in RCTs?

- Perceived or actual barriers to warfarin use:
  - Alcohol abuse (ETOH)
  - Cirrhosis/Hepatitis
  - Intracranial hemorrhage
  - Gastrointestinal or genitourinary hemorrhage
  - Other hemorrhage
  - Predisposition to falls (Falls)
  - Renal insufficiency (RI)

    any time before or on the AF index date
    - ICD9 codes
    - RMRS dictionary terms (Gopher system has drop-down menus with diagnoses, etc)

Source: Rosenman, ESC and AHA 2009

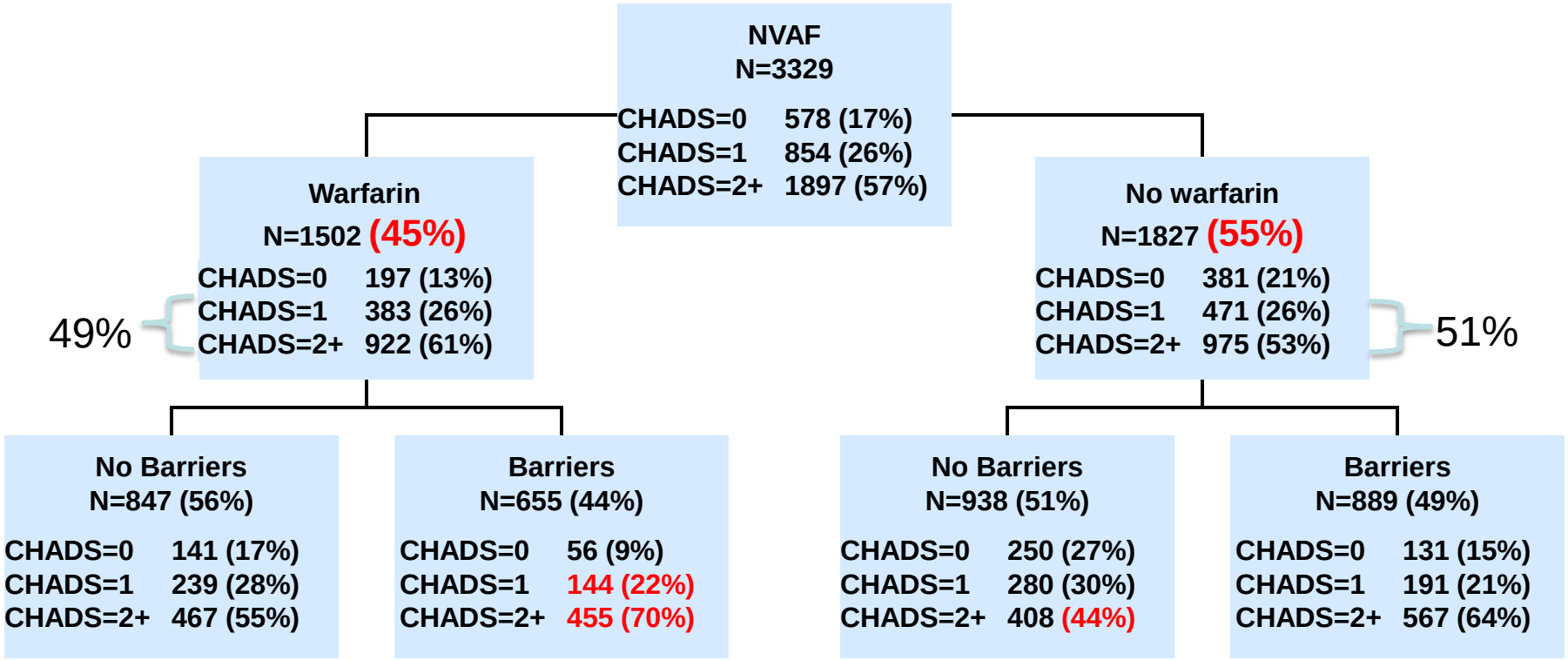
Methods: Risk Adjustments

Risk Score / Factor (points)	$CHADS_2$	CHA_2DS_2 – VASc
Congestive heart failure	1	1
Hypertension	1	1
Age > 75 years	1	2
Diabetes mellitus	1	1
Prior **S**troke or TIA	2	2
Vascular disease (Previous MI, PAD, aortic plaque)		1
Age (65-74)		1
Sex **c**ategory (female)		1

HASBLED & CHADS-VASc: Apps – MedCalc 2.5, P Pfiffner

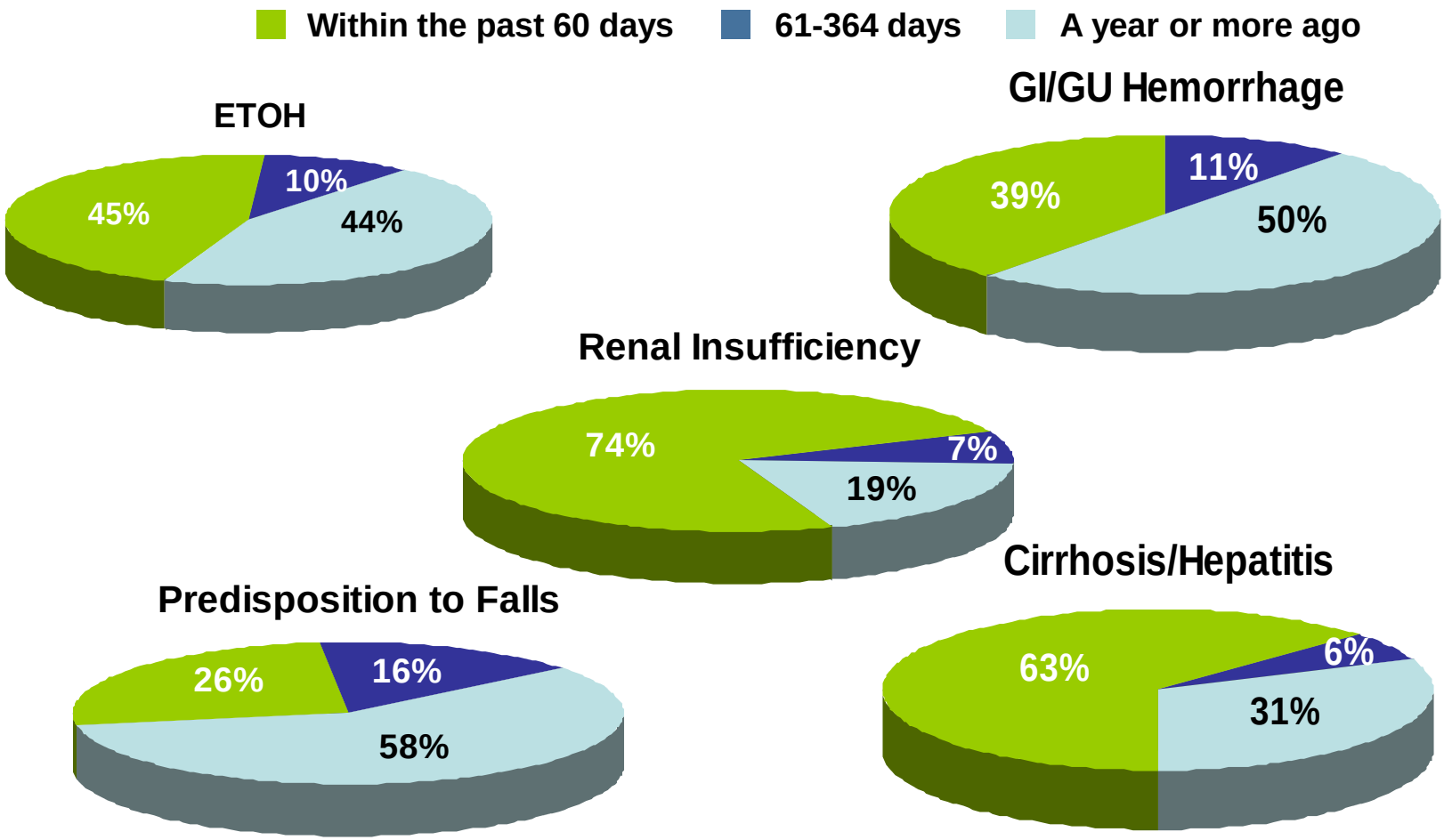
Odem LE, et.al. *Pharmacotherapy* 2012;32(3):285-296

Results: Perceived or Actual Barriers by Exposure to Warfarin by $CHADS_2$ Score



Source: Rosenman, ESC and AHA 2009

Results: How long before the AF index date was the most recent record of the barrier? (N=599 exposed to warfarin, and with CHADS2 > 0)



Source: Rosenman, ESC and AHA 2009

Outcomes Research: The Purpose

To determine:

- Do patients benefit?
  - Warfarin works – RCTs = 68 % Relative Risk Reduction (RRR) of Strokes
  - But in the REAL WORLD
    - ~40 % UNTREATED
    - ~27 % GOOD QUALITY OF CARE
    - Many BARRIERS to effective care
      - REAL or IMAGINED

Agency for Health Care Policy & Research, 1990
Agency for Healthcare Research and Quality, 2003

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

Warfarin-Control Phase III

Current Trials of Antithrombotic Therapy for Stroke Prevention in Atrial Fibrillation

Trial	Agent	Blind	CHADS	Size
RE-LY	Dabigatran	OL	≥ 1	18,000
ROCKET	Rivaroxaban	DB	≥ 2-3	14,000
ARISTOTLE	Apixaban	DB	≥ 1	15,000
ENGAGE	Endoxaban	DB	≥ 2	20,000
Total				66,000

AF Historical trials: **3,763**

AF Trials: Key Design Issues

- Superiority vs. non-inferiority?
    - Non-inferiority margin
- Open-label (PROBE) vs. double-blind (DB)?
- Dosing issues for benefit, for risk (e.g. renal)
- Benefit-risk tolerances
- Extrapolations for populations at risk

See: Jessica Mega's *NEJM* (28 Aug 11) editorial and Kevin Jackson's *AHJ* (2008) article!

RE-LY

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 17, 2009 VOL. 361 NO. 12

Dabigatran versus Warfarin in Patients with Atrial Fibrillation

Stuart J. Connolly, M.D., Michael D. Ezekowitz, M.B., Ch.B., D.Phil., Salim Yusuf, F.R.C.P.C., D.Phil., John Eikelboom, M.D., Jonas Oldgren, M.D., Ph.D., Amit Parekh, M.D., Janice Pogue, M.Sc., Paul A. Reilly, Ph.D., Ellison Themeles, B.A., Jeanne Varrone, M.D., Susan Wang, Ph.D., Marco Alings, M.D., Ph.D., Denis Xavier, M.D., Jun Zhu, M.D., Rafael Diaz, M.D., Basil S. Lewis, M.D., Harald Darius, M.D., Hans-Christoph Diener, M.D., Ph.D., Campbell D. Joyner, M.D., Lars Wallentin, M.D., Ph.D., and the RE-LY Steering Committee and Investigators*

1. **Dabigatran 150 mg, BID**
2. **Dabigatran 110 mg, BID**
3. **Warfarin INR 2 to 3 range**

Courtesy: Dr. G Merli

Connolly S, et al *NEJM* 2009;361:1139-1151

ROCKET AF

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 8, 2011 VOL. 365 NO. 10

Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation

Manesh R. Patel, M.D., Kenneth W. Mahaffey, M.D., Jyotsna Garg, M.S., Guohua Pan, Ph.D., Daniel E. Singer, M.D., Werner Hacke, M.D., Ph.D., Günter Breithardt, M.D., Jonathan L. Halperin, M.D., Graeme J. Hankey, M.D., Jonathan P. Piccini, M.D., Richard C. Becker, M.D., Christopher C. Nessel, M.D., John F. Paolini, M.D., Ph.D., Scott D. Berkowitz, M.D., Keith A.A. Fox, M.B., Ch.B., Robert M. Califf, M.D., and the ROCKET AF Steering Committee, for the ROCKET AF Investigators*

Rivaroxaban 20 mg, Qday

Warfarin INR 2-3 Range

Courtesy: Dr. G Merli

Patel **M et al, *NEJM* 2011;365:883-891**

ARISTOTLE

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 15, 2011 VOL. 365 NO. 11

Apixaban versus Warfarin in Patients with Atrial Fibrillation

Christopher B. Granger, M.D., John H. Alexander, M.D., M.H.S., John J.V. McMurray, M.D., Renato D. Lopes, M.D., Ph.D.
Elaine M. Hylek, M.D., M.P.H., Michael Hanna, M.D., Hussein R. Al-Khalidi, Ph.D., Jack Ansell, M.D., Dan Atar, M.D.,
Alvaro Avezum, M.D., Ph.D., M. Cecilia Bahit, M.D., Rafael Diaz, M.D., J. Donald Easton, M.D.,
Justin A. Ezekowitz, M.B., B.Ch., Greg Flaker, M.D., David Garcia, M.D., Margarida Geraldes, Ph.D.,
Bernard J. Gersh, M.D., Sergey Golitsyn, M.D., Ph.D., Shinya Goto, M.D., Antonio G. Hermosillo, M.D.,
Stefan H. Hohnloser, M.D., John Horowitz, M.D., Puneet Mohan, M.D., Ph.D., Petr Jansky, M.D., Basil S. Lewis, M.D.
Jose Luis Lopez-Sendon, M.D., Prem Pais, M.D., Alexander Parkhomenko, M.D., Freek W.A. Verheugt, M.D., Ph.D.,
Jun Zhu, M.D., and Lars Wallentin, M.D., Ph.D., for the ARISTOTLE Committees and Investigators*

Apixaban 5 mg, BID
Warfarin INR 2 - 3

Courtesy: Dr. G Merli

Granger C, et al *NEJM* 2011;365:981-992

Comparison of Oral Anticoagulants*

Generic name	warfarin	dabigatran	rivaroxiban	apixaban
Brand name	Coumadin	Pradaxa	Xarelto	Eliquis
Half-Life (hours)	40	12-14	7-10	12
Renal Clearance %	0	80	35	25
Dose	Once a day	Twice a day	Once a day	Twice a day
Approx $/pill	$0.64	$4.37 bid	$8.75	>$4.50 bid

*Granger and Armaganijan, *Circ* 2012;125:159-64.
Bilazarian, theheart.org, July 5, 2012.

Comparison of oral anticoagulants – baseline*

Baseline Data	warfarin	dabigatran	rivaroxiban	apixaban
Trials	5 major trials	RE-LY, *NEJM* 2009	ROCKET, *NEJM* 2011	ARISTOTLE, *NEJM* 2011
Age (years)		71	73	70
$CHADS_2$ (mean)		2.2	3.5	2.1
$CHADS_2$ 3-6 (%)		32	87	30
Prior stroke (%)		20	55	19
Prior warfarin (%)		50	62	57

* Lip GYH, et.al. *JACC* 2012;60:738-46

Comparison of oral anticoagulants – outcomes*

Annual Incidence – rate per 100 person-years

	warfarin	dabigatran (150 mg)	rivaroxiban	apixaban
Trial Results (*P* ◆)	Versus placebo-asa	Versus warfarin	Versus warfarin	Versus warfarin
Stroke or systemic emb	1.4 v. 4.7 ◆	1.11 v. 1.71◆	2.12 v. 2.42	1.27 v. 1.60 ◆
Hemorrhagic stroke		0.1 v. 0.38 ◆	0.5 v. 0.7 ◆	0.24 v. 0.47 ◆
Ischemic stroke		0.92 v. 1.20 ◆	NR	0.97 v. 1.05
Major bleeding (on treatment)	1.6 v. 1.0 ◆	3.11 v. 3.36	3.6 v. 3.45	2.13 v. 3.09 ◆
All cause death		3.64 v. 4.13	4.5 v. 4.9	3.52 v. 3.94 ◆

NR – not reported

* Granger and Armaganijan, *Circ* 2012;125:159-64.

Lip GYH, et.al. *JACC* 2012;60:738-46.

Comparison of oral anticoagulants – % RRR*

Relative Risk Reduction (RRR)

	warfarin	dabigatran (150 mg)	rivaroxiban	apixaban
Trial Results (RRR; *P* ◆)	Versus placebo-asa	Versus warfarin	Versus warfarin	Versus warfarin
Stroke or systemic emb	68 % ◆	34 % ◆	12 %	21 % ◆
Hemorrhagic stroke		74 % ◆	41 % ◆	49 % ◆
Ischemic stroke		24 % ◆	6 %	8 %
Major bleeding		7 %	104 %	31 % ◆
All cause death		12 %	8 %	11 % ◆

* Granger and Armaganijan, *Circ* 2012;125:159-64.
Lip GYH, et.al. *JACC* 2012;60:738-46.

Caveats Relating to Published Trials Concerning Hemorrhage

Randomized trials

- Enrolled few patients ≥ 80 years
- Highly selected, closely monitored
- Vitamin K antagonist at entry

Prospective cohort studies

- Predominantly non-inception cohort studies of prevalent warfarin use (survivor bias)
- Enrolled few patients ≥ 80 years
- Varying definitions of bleeding

Danger Ahead:
Watch Out for Indirect Comparisons!*

- Use Extreme Caution – e.g. Fibrinolytics misleading
- Potential Mitigating Issues with Anticoagulants:
  - Trial designs
  - Event rates (e.g. MI and Bleeding)
  - $CHADS_2$ Risk Cohorts
  - INR – TTR (Time in Therapeutic Range)
  - Regulatory Considerations, for example:
    - Dabigatran - 110 mg not approved
      - bleeding vs. warfarin - similar
    - Rivaroxiban - Stroke and bleeding vs. warfarin - similar
    - Apixaban - Mortality vs. warfarin - superior

* Cannon and Kohi, *JACC* 2012;60:747-8

Pooled Indirect Comparisons: DABI, RIVA and APIX versus Warfarin*

Stroke or Systemic Embolism	↓ 21% (p<0.001)
Stroke	↓ 23% (p<0.001)
Hemorrhagic Stroke	↓ 53% (p<0.001)
All Cause Mortality	↓ 12% (p<0.001)
Major Bleeding	↓ 13% (p<0.001)

* Lip GYH et.al, *JACC* 2012;60:738-46

Indirect Comparisons: CAUTION

- Lip GYH, et al. *JACC* 2012;60:738-746
  - **Stroke / sys emb: DABI better RIVA (by 26%)**
  - **Ischemic stroke, no significant differences**
  - **Major bleeding: APIX < $DABI_{150}$ 26%; < RIVA 34%; = $DABI_{110}$**
  - **No profound significant differences in efficacy**
    - **safety – better for APIX or $DABI_{110}$**

- Schneeweiss S, et al. *Circ CV Qual Outcomes* 2012;5:480-486
  - **$CHADS_2 \geq 3$ – ADJUSTMENT: DABI 150 vs. APIX vs. RIVA**
  - **For efficacy, no significant differences**
    - **although DABI & APIX numerically better RIVA**
  - **For major hemorrhage, APIX less than DABI or RIVA**
  - **Until head-to-head trials, adjusted indirect comparisons are one tool to guide initial therapeutic choices**

Outcomes Research: The Purpose

To determine:

- What treatments work best?
  - RCT EVIDENCE: RE-LY, ROCKET-AF, ARISTOTLE
    - NOACs superior to warfarin
    - First viable alternatives in 50 years
  - Real World Studies ????
    - Usual Care: Safety and Effectiveness
    - Monitoring
    - Cost

Agency for Health Care Policy & Research, 1990
Agency for Healthcare Research and Quality, 2003

Recent Literature: Commentaries

- Ansell J, *Circ* 2012;125:165-170
  - **Time in Therapeutic Range is important to effectiveness**
  - **Short T½, has implications for adherence and stroke risk**
  - **No monitoring has implications for safety**
  - **No antidote for emergent situations**
  - **Cost**

- Spinler SA and Shafir V, *Circ* 2012;126:133-137
  - **Pharmacy perspective; case study approach; easy read**
  - **P-450 system and CYP3A4 metabolic implications**
    - **Drug-drug interactions, renal disease adjustments**
  - **Switching therapies**
  - **Combined use of other anticoagulants (UFH, LMWH…)**

Novel Anticoagulant Comparison

	Dabigatran	*Rivaroxaban*	*Apixaban*
Dialyzable	Yes	Probably Not	Probably Not
Protein Binding	35%	>90%	87%
Reversing Agent	No	Possibly	Possibly

Courtesy: Dr. G Merli

Erikkson BI, et al. *Clin Pharmacokinet* 2009;48:1-22.

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

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Reversal of Rivaroxaban and Dabigatran by Prothrombin Complex Concentrate : A Randomized, Placebo-Controlled, Crossover Study in Healthy Subjects

Elise S. Eerenberg, Pieter W. Kamphuisen, Meertien K. Sijpkens, Joost C. Meijers, Harry R. Buller and Marcel Levi

Courtesy: Dr. G Merli

Eerenberg E, et al *Circulation* 2011;124:1573-1579

Package Insert Recommendations

- Dabigatran
  - FFP, Prothrombin Complex Concentrate
  - Activated Factor VII
  - Dialysis
- Rivaroxaban and Apixaban
  - Prothrombin Complex Concentrate
  - FFP

Courtesy: Dr. G Merli

AF Evidence: Key Practice Issues

- Well controlled vs. usual care?
- Controlling barriers to effective care:
    - Patient medical characteristics (elderly…)
    - Patient capabilities (logistics…) and comprehension (instructions, risk…)
    - Systems (MD/office logistics, testing, $, legal…)
    - Therapeutic motivations (Pt/Carer/MD/RN/PharmD)
- Net clinical benefit - tradeoffs?
    - For the patient…, For the family…
    - For the providers…, For the system…
    - Value assessments, for whom…

Source: Ingelgard A, et al. *J Thromb Thrombolysis. 2006;*21(3):257-265

Outcomes Research: The Purpose

To determine:

- Are health-care resources well spent?
  - Cost Offsets
  - REAL WORLD Scenarios
- Concluding thoughts

Agency for Health Care Policy & Research, 1990
Agency for Healthcare Research and Quality, 2003

Comparison of Oral Anticoagulants – continued*

Average medical costs in $/patient/year

	warfarin	dabigatran	rivaroxiban	apixaban
Ischemic Stroke	490	373	461	451
Hemorrhagic stroke	225	59	133	115
Systemic emb	40	38	17	33
MI	292	371	237	257
Major bleed	998	1030	1106	715
CRN-M bleed	38	35	41	26
TOTAL	**2084**	**1905**	**1995**	**1599**
Savings vs warfarin	-----	**179**	**89**	**485**

CRN-M Bleed – Clinically relevant non-major bleed

* Deitelzweig, S, et.al. Ochsner Clinic, New Orleans, LA, American College of Cardiology, April, 2012, Chicago, IL

Intervention Scenarios Representing Actual Practice Management / Outcomes*

Intervention	Stroke Rate	Bleeding Rate	INR compliance	Discontinuation rates	CEA v. warfarin +
Warfarin Poor	higher	higher	poor	poor	+++
Warfarin Fair	high	high	fair	fair	++
Warfarin Good	Low	low	good	minimal	– / +
ASA	Higher	low	NA	minimal	+++
No Therapy	highest	some	NA	NA	+++
No Therapy post DC	highest	some	NA	100%	++++

*Estimated from literature, see notes

CEA v. warfarin, plus : + Potential for positive findings

The CLOT BLOG on theheart.org

FDA approval of *the latest NOAC* for stroke prevention in AF: The "tipping point" for novel oral anticoagulants

January 11, 2013

Samuel Z. Goldhaber, MD
Professor of Medicine, Harvard Medical School
Director, Venous Thromboembolism Research Group
Co-Director, Anticoagulation Management Service
Cardiovascular Division, Brigham and Women's Hospital, Boston, MA

Concluding Thoughts

- Effective drugs are usually cost-effective
- Well-controlled trials suggest superiority of NOACs, BUT…
- Real world experience is needed! Issues to watch:
  - Non-trial subjects (elderly, renal, falls…)
  - Emergent situations (bleeding and risk)
  - Usual Care: Adherence, DDIs, dosing, switching…
  - Afib and ACS (WOEST at ESC 2012)
    - clopidogrel + warfarin > aspirin + clopi + warf
      - yielded better efficacy and less bleeding
- Other uses: Surgery-medical VTEp, DVT, PE, ACS and valves?

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